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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,258	11/28/2006	Dong Wang	21101.0130U2	8266

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EXAMINER	
FOLEY, SHANON A	
ART UNIT	PAPER NUMBER
1619	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,258	WANG ET AL.	
	Examiner	Art Unit	
	SHANON A. FOLEY	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-18,20-32,34-39,41,42,44-47,49-54 and 57-66* is/are pending in the application.

4a) Of the above claim(s) *16-18,20-32,34-39,41,42,44-47,49-54 and 62-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-15 and 57-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I and the species elections of: (a) a HPMA copolymer; (b) peptides; (c) N-(2-hydroxypropyl)methacrylamide; and (d) glucocorticoids in the reply filed on November 29, 2010 is acknowledged.

Claims 1, 2, 4-18, 20-32, 34-39, 41, 42, 44-47, 49-54 and 57-66 are pending; claims 16-18, 20-32, 34-39, 41, 42, 44-47, 49-54 and 62-67 are withdrawn due to non-elected subject matter; and claims 1, 2, 4-15 and 57-61 are under consideration.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on August 30, 2006 has been considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5, 8 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodle et al. (US 5,356,633) and Metselaar et al. (Arthritis and Rheumatism. 2003; 48 (7): 2059-2066).

Woodle et al. teach compositions comprising a hydrophilic biocompatible polymer, polyethylene glycol (PEG), in combination with anti-inflammatory therapeutic agents, such as

NSAIDs, see column 4, lines 9-25. The composition is formulated such that upon administration, it concentrates in a predetermined site, see column 4, lines 32-50.

Woodle et al. do not teach the preferred anti-inflammatory agent, glucocorticoids, or incorporating a bio-assay label.

However, Metselaar et al. teach incorporating glucocorticoids into PEG liposomes, see "Preparations" bridging the columns on page 2060. Metselaar et al. also teach use of a radioactive ^{111}In-oxine label incorporated into the PEG liposomes, see the paragraph bridging pages 2060-2061, to determine tissue distribution of the glucocorticoid-loaded PEG-liposomes, see "Tissue distribution" on page 2062.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate glucocorticoids of Metselaar et al. into the inflammatory treatment formulation of Woodle et al. with a reasonable expectation of success because glucocorticoids are conventional for the treatment of arthritis; the incorporation of glucocorticoids into the formulation of Woodle et al. would have achieved rapid anti-inflammatory effects and specific accumulation at the site of inflammation; see Figures 3 and 4 on page 2063 and "Tissue Distribution" on page 2062 of Metselaar et al.

While neither Woodle et al. nor Metselaar et al. teach the PEG directly linked to the anti-inflammatory agent, Woodle et al. do teach derivatized lipids wherein the lipid is linked to the polymer, see column 7, lines 14-44 and Metselaar et al. teach PEG-DSPE conjugates, see "Preparations" bridging the columns on page 2060. In addition, Metselaar et al. do not teach direct linkage of the bio-assay label to the water-soluble polymer.

However, it would have been reasonable to link the drug and polymers directly to optimize therapeutic efficacy. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to directly link the anti-inflammatory drug to the carrier to ensure targeted delivery and accumulation at the inflamed areas, see "Tissue Distribution" on page 2062 of Metselaar et al. Further, one of ordinary skill in the art at the time the invention was made would have been motivated to directly link the bio-assay label to the carrier (linked to the drug) to eliminate background 'noise' detection from stray labels.

Claims 2, 4, 6, 7, 9-14 and 57-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodle et al. and Metselaar et al. as applied to claims 1, 4, 5, 8 and 15 above, and further in view of Omelyanenko et al. (Journal of Controlled Release. 1998; 53: 25-37) and Smolen et al. (Nature Reviews. June, 2003; 2: 473-488).

See the teachings of Woodle et al. and Metselaar et al. above. Neither reference teaches: 1) an HPMA copolymer-drug conjugate; 2) using cleavable or uncleavable spacers between the therapeutic agent and the water-soluble polymer or between the targeting moiety and the water-soluble polymer; 3) a specific targeting moieties that target a plurality of tissues; 4) a plurality of therapeutic agents; or 5) a plurality of distinct bio-assay labels.

Omelyanenko et al. teach various conjugates using targetable N-(2-hydroxypropyl)-methyacrylamide (HPMA) copolymer linked to anti-cancer drug adriamycin (ADR) by a biodegradable (cleavable) spacer, GFLG, or a non-degradable (un-cleavable) spacer, GG. These complexes are linked to targeting moieties, N-acylated galactosamine (GalN) or monoclonal antibody, OV-TL16 in human carcinoma HepG2 and ovarian carcinoma OVCAR-3 cells, respectively. See the paragraph bridging the columns of page 26 and section 2.2 Synthesis of

HPMA copolymers on page 27. Omelyanenko et al. also teaches uses a plurality of distinct bio-assay labels bound to the conjugate, FITC, or use of the intrinsic fluorescence of adriamycin, see the paragraph bridging the columns on page 26.

One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the HPMA copolymer carrier of Omelyanenko et al. for the PEG liposomes of Woodle et al. and Metselaar et al., with a reasonable expectation of success, to enhance subcellular delivery and therapeutic efficacy of the drug, see the last full paragraph of the first column on page 26 of Omelyanenko et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to use the biodegradable and/or non-degradable spacers of Omelyanenko et al. to link the HPMA copolymer with the active agent of Metselaar et al. or Woodle et al. and the targeting moiety, as taught by Omelyanenko et al., to maintain drug-copolymer interaction until intracellular delivery, see the first full paragraph on page 26 of Omelyanenko et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to use multiple bio-assay labels in the HPMA conjugate of Woodle et al., Metselaar et al. and Omelyanenko et al., to monitor the liberation of the active agent from the carrier intracellularly and further, into the nucleus, see section 2.3 Subcellular trafficking of conjugates, bridging pages 27-28, as well as sections 3.1 and 3.2, bridging pages 30-33 of Omelyanenko et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to use multiple therapeutic agents in the treatment of arthritis because Smolen et al. teach that treatment efficacy of rheumatoid arthritis is enhanced using combination therapies, see

the two full paragraphs of the second column on page 476 of Smolen et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for using the multiple therapeutic agents, outlined by Smolen et al. in the formulation of Woodle et al., Metselaar et al. and Omelyanenko et al. because both formulations of Woodle and Metselaar et al. are used to treat arthritis, see the previous citations of Metselaar et al. and column 22, lines 9-35 of Woodle et al.

Lastly, one of ordinary skill in the art at the time the invention was made would have been motivated to use multiple targeting moieties, as taught by Omelyanenko et al., (including bone or cartilage targeting moieties) in the combined conjugate of Woodle et al., Metselaar et al. and Omelyanenko et al. to target the various joints and tissues affected by RA, see the second paragraph of the first column on page 473 and Figure 1 on page 474 of Smolen et al.

Claims 1, 2 and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Bioconjugate Chemistry. 2003; 14: 853-859) and Metselaar et al. (Arthritis and Rheumatism. 2003; 48 (7): 2059-2066).

Wang et al. teach water-soluble HPMA copolymer conjugates comprising bone-targeting compounds, alendronate and aspartic acid peptide and bio-assay label, FITC. The bone therapeutics were covalently attached to the HPMA copolymer carrier by acid or enzymatic cleavable and uncleavable spacer (-GG-). See the abstract, the paragraph bridging pages 853-854, as well as the second and third paragraphs of the second column on page 854.

Wang et al. do not teach delivering therapeutic agents.

However, Metselaar et al. teach incorporating glucocorticoids into PEG liposomes, see "Preparations" bridging the columns on page 2060.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate glucocorticoids of Metselaar et al. into the HPMA copolymer conjugate of Wang et al. to deliver the arthritis treatment agent specifically to the targeted tissue. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for incorporating glucocorticoids into the HPMA copolymer conjugate of Wang et al. because Wang et al. teach an additional copolymer PEG conjugate and the bone-targeting capability of the conjugates of Wang et al. would be advantageous for the treatment of arthritis, see "Tissue distribution" on page 2062 of Metselaar et al.

Claims 57-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. and Metselaar et al. as applied to claims 1, 2 and 4-15 above, and further in view of Smolen et al. and Omelyanenko et al.

See the teachings of Wang et al. and Metselaar et al. above. Neither reference teaches using a plurality of distinct therapeutic agents, targeting moieties to target a plurality of tissues or using a plurality of bio-assay labels.

Omelyanenko et al. teach various conjugates using targetable N-(2-hydroxypropyl)-methyacrylamide (HPMA) copolymer linked to anti-cancer drug adriamycin (ADR) by a biodegradable (cleavable) spacer, GFLG, or a non-degradable (un-cleavable) spacer, GG. These complexes are linked to targeting moieties, N-acylated galactosamine (GalN) or monoclonal antibody, OV-TL16 in human carcinoma HepG2 and ovarian carcinoma OVCAR-3 cells, respectively. See the paragraph bridging the columns of page 26 and section 2.2 Synthesis of HPMA copolymers on page 27. Omelyanenko et al. also teaches uses a plurality of distinct bio-

assay labels bound to the conjugate, FITC, or use of the intrinsic fluorescence of adriamycin, see the paragraph bridging the columns on page 26.

One of ordinary skill in the art at the time the invention was made would have been motivated to use multiple bio-assay labels, taught by Omelyanenko et al. in the HPMA conjugate of Wang et al. to monitor the liberation of the active agent from the carrier intracellularly and further, into the nucleus, see section 2.3 Subcellular trafficking of conjugates, bridging pages 27-28, as well as sections 3.1 and 3.2, bridging pages 30-33 of Omelyanenko et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to use multiple therapeutic agents in the conjugate of Wang et al., Metselaar et al. and Omelyanenko et al., in the treatment of arthritis because Smolen et al. teach that treatment efficacy of rheumatoid arthritis is enhanced using combination therapies, see the two full paragraphs of the second column on page 476 of Smolen et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for using the multiple therapeutic agents, outlined by Smolen et al., in the conjugate of Wang et al., Metselaar et al. and Omelyanenko et al. because both conjugates of Wang et al. and Metselaar et al. target bone tissue, see the previous citations of Wang et al. and "Tissue distribution" on page 2062 of Metselaar et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to use multiple targeting moieties, as taught by Omelyanenko et al. in the combined conjugate of Wang et al. and Metselaar et al. to target the various joints and issues affected by RA, see the second paragraph of the first column on page 473 and Figure 1 on page 474 of Smolen et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHANON A. FOLEY whose telephone number is (571)272-0898. The examiner can normally be reached on flex, generally M-F 7AM - 3 PM, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne L. Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shanon A. Foley/
Primary Examiner
Art Unit 1619